

# <sup>13</sup>C urea breath test for *Helicobacter pylori*: Evaluation of 10-minute breath collection

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M Mauro, V Radovic, M Wolfe, M Kamath, P Bercik, D Armstrong. <sup>13</sup>C urea breath test for *Helicobacter pylori*: Evaluation of 10-minute breath collection. *Can J Gastroenterol* 2006;20(12):775-778.

**AIM:** To determine whether a shortened <sup>13</sup>C urea breath test (<sup>13</sup>C UBT) (breath collection time of 10 min) is as reliable as the standard assay (30 min).

**METHODS:** Two hundred ninety-seven patients (mean ± SD: 53±16 years, 57% female) completed a <sup>13</sup>C UBT. Breath samples were obtained at baseline and at 5 min intervals up to 30 min. Sixty-seven patients also underwent endoscopic biopsy. Cluster analysis was performed on the <sup>13</sup>C UBT data to determine the optimal cut-off point at each time interval. Sensitivity and specificity of the <sup>13</sup>C UBT at all intervals compared with histology and culture and against the standard 30 min interval were determined.

**RESULTS:** The calculated optimal cut-off points for each time interval (T), expressed as delta over baseline (δ‰), were 3.29 δ‰ at T<sub>5</sub>, 3.15 δ‰ at T<sub>10</sub>, 3.42 δ‰ at T<sub>15</sub>, 3.17 δ‰ at T<sub>20</sub>, 2.99 δ‰ at T<sub>25</sub> and 2.82 δ‰ at T<sub>30</sub>. Except at T<sub>5</sub>, the risk of false-positive and false-negative test results at each time interval was lower than 2.3% using these cut-off points. When replacing the cut-off points with 3.0 δ‰, the risk of error was still lower than 2.3%. The test at T<sub>10</sub> showed 98.6% sensitivity and 98.6% specificity compared with T<sub>30</sub>. T<sub>10</sub> and T<sub>30</sub> showed 100% sensitivity and 96% specificity compared with histology and culture.

**CONCLUSIONS:** The <sup>13</sup>C UBT is an accurate, noninvasive test, even when the breath sample interval is reduced to 10 min. The present study confirms the validity of a cut-off point of 3.0 δ‰ for the 10 min and 30 min <sup>13</sup>C UBT.

**Key Words:** <sup>13</sup>C urea breath test; Cut-off point; *Helicobacter pylori*

*Helicobacter pylori* infection is one of the most common human infections worldwide (1). Although the prevalence of *H pylori* is falling in the western world, the prevalence in Canada still remains in the range of 20% to 40% (2,3). Since the discovery of the *H pylori* association with chronic gastritis, peptic ulcers, gastric lymphoma and gastric adenocarcinoma (4-6), several diagnostic tests, both invasive and noninvasive, have been developed. The development of the <sup>13</sup>C urea breath test (<sup>13</sup>C UBT), which has a specificity of 98% and a sensitivity of 97%, allows the determination of *H pylori* status without the need for costly invasive endoscopies (7).

## Le test respiratoire à l'urée marquée au <sup>13</sup>C pour dépister l'*Helicobacter pylori*: L'évaluation d'un prélèvement d'air expiré de 10 minutes

**OBJECTIF :** Déterminer si un test respiratoire à l'urée marquée au <sup>13</sup>C (TRUM <sup>13</sup>C) moins long (prélèvement d'air expiré de 10 minutes) est aussi fiable que le test standard (30 minutes).

**MÉTHODOLOGIE :** Deux cent quatre-vingt-dix-sept patients (âge moyen de 53±16 ans, 57 % de sexe féminin) ont subi un TRUM <sup>13</sup>C. On a prélevé l'air expiré au début du test, puis à intervalles de cinq minutes jusqu'à 30 minutes. Soixante-sept patients ont également subi une biopsie endoscopique. On a exécuté une analyse typologique des données du TRUM <sup>13</sup>C pour déterminer la limite d'inclusion optimale à chaque intervalle. On a également déterminé la sensibilité et la spécificité du TRUM <sup>13</sup>C à chaque intervalle par rapport à l'histologie, à la culture et à l'intervalle de 30 minutes.

**RÉSULTATS :** Les limites d'inclusion optimales calculées à chaque intervalle (T), exprimées à titre de coefficient delta sur le temps de base (δ‰) étaient de 3,29 δ‰ au T<sub>5</sub>, de 3,15 δ‰ au T<sub>10</sub>, de 3,42 δ‰ au T<sub>15</sub>, de 3,17 δ‰ au T<sub>20</sub>, de 2,99 δ‰ au T<sub>25</sub> et de 2,82 δ‰ au T<sub>30</sub>. D'après ces limites d'inclusion, sauf au T<sub>5</sub>, le risque de résultats faux positifs ou faux négatifs à chaque intervalle était inférieur à 2,3 %. Lorsqu'on remplaçait les limites d'inclusion par 3,0 δ‰, le risque d'erreur demeurait inférieur à 2,3 %. Le test au T<sub>10</sub> a révélé une sensibilité de 98,6 % et une spécificité de 98,6 % par rapport au T<sub>30</sub>. Les tests aux T<sub>10</sub> et T<sub>30</sub> ont révélé une sensibilité de 100 % et une spécificité de 96 % par rapport à l'histologie et à la culture.

**CONCLUSIONS :** Le TRUM <sup>13</sup>C est un test précis et non effractif, même lorsque l'intervalle de prélèvement d'air expiré est réduit à 10 minutes. La présente étude confirme la validité d'utiliser une limite d'inclusion de 3,0 δ‰ pour le TRUM <sup>13</sup>C à 10 minutes et à 30 minutes.

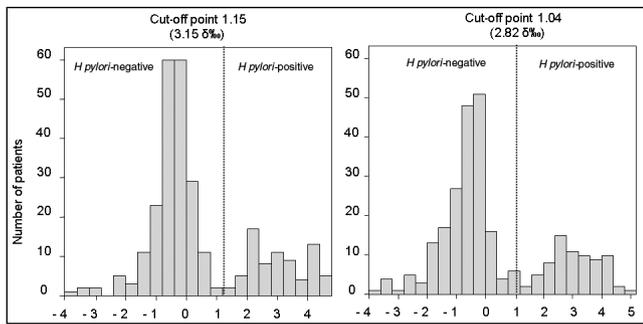
The <sup>13</sup>C UBT has become the noninvasive test of choice for both diagnosis and for confirmation of *H pylori* eradication after treatment, as recommended by a number of clinical guidelines (8-10). The <sup>13</sup>C UBT is a practical and accurate test on which to base a 'test and treat' strategy for dyspepsia management (11,12) and its clinical performance has recently been validated in Canada in a community laboratory setting (pages 770-774 in the current issue of the *Journal*).

The <sup>13</sup>C UBT detects gastric *H pylori* urease activity by measuring <sup>13</sup>C enrichment in expired breath samples after ingestion of <sup>13</sup>C-labelled urea. There is general agreement on

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**Figure 1**) Cluster analysis. The histogram of the logarithmically transformed  $^{13}\text{C}$  urea breath sample values at 10 min past baseline and 30 min past baseline showed two distinct populations: *Helicobacter pylori*-negative and *H pylori*-positive. The cut-off value for each sample interval was calculated as the point equidistant between the means of the *H pylori*-negative and *H pylori*-positive populations

the use of two breath samples, one collected before and another 30 min after urea ingestion, regardless of the dosage of the isotope administered.

In view of the increasing application of  $^{13}\text{C}$  UBT due to the large number of individuals who may have an *H pylori* infection, a rapid performance of  $^{13}\text{C}$  UBT may be advantageous to patients and health services to reduce costs and personnel utilization.

The aim of the present study was to compare the accuracy of a 10 min breath collection with the standard 30 min breath collection for the  $^{13}\text{C}$  UBT, and to compare the short-course  $^{13}\text{C}$  UBT with histology and culture.

## PATIENTS AND METHODS

The study protocol was approved by the McMaster University Research Ethics Board. The  $^{13}\text{C}$  UBT was performed in 297 patients (mean age  $\pm$  SD:  $53 \pm 16$  years, 57% female) who had various gastrointestinal symptoms. One hundred twenty-two patients were tested to evaluate the primary diagnosis of *H pylori* infection (diagnosis group) and 60 were tested for confirmation of eradication after therapy (post-treatment group); 115 patients were referred without being categorized in either group.

Patients were asked about their use of antibiotics and acid-suppressive treatment during the four weeks before the testing and about previous eradication therapy. Exclusion criteria included the use of proton-pump inhibitors, bismuth compounds or antibiotics within 14 days before the  $^{13}\text{C}$  UBT.

After an overnight fast, patients performed the  $^{13}\text{C}$  UBT by providing breath samples at baseline ( $T_0$ ) and at 5 min intervals up to 30 min ( $T_5$ ,  $T_{10}$ ,  $T_{15}$ ,  $T_{20}$ ,  $T_{25}$  and  $T_{30}$ ) after oral ingestion of 75 mg  $^{13}\text{C}$ -labelled urea (Helikit, Isotechnika Diagnostics, Canada) in 100 mL of citric acid solution. All samples were analyzed by a gas isotope ratio mass spectrometer (BreathMAT, Finnigan MAT GmbH, Germany). The difference between the values at  $T_5$ ,  $T_{10}$ ,  $T_{15}$ ,  $T_{20}$ ,  $T_{25}$  and  $T_{30}$  and those at  $T_0$  are expressed as delta over baseline (DOB,  $\delta\%$ ). Based on prior validation (13), the cut-off point for the diagnostic test was defined as 3.0  $\delta\%$ .

Data were examined visually by plotting the logarithmic transformation of measurements taken from the  $^{13}\text{C}$  UBT at  $T_5$ ,  $T_{10}$ ,  $T_{15}$ ,  $T_{20}$ ,  $T_{25}$  and  $T_{30}$ . The distribution of the natural logarithms (logn) of the DOB values at each breath sample test interval identified

two normally distributed subpopulations that were considered to represent *H pylori*-positive and *H pylori*-negative patients. The normal distribution of the positive and negative populations enabled cluster analysis to be performed on these data to determine the minimal intraclass variance, and thus, the logn ( $T_{\text{sample interval}} - T_0$ ) value, which best separated the presumed *H pylori*-negative and *H pylori*-positive populations. Thereafter, the parameters (mean DOB and SD) of the *H pylori*-negative and *H pylori*-positive populations were established. The cut-off value was calculated as the point equidistant from the means of *H pylori*-negative and *H pylori*-positive populations. Thus, the probability an *H pylori*-negative patient producing a  $^{13}\text{C}$  UBT result with a value greater than the cut-off point (ie, a false-positive result), and the probability of an *H pylori*-positive patient producing a  $^{13}\text{C}$  UBT result with a smaller value than the cut-off point (ie, a false-negative result) were determined. This analysis was performed on the total patient group and on the diagnosis and post-treatment subgroups at each breath sample test interval. Sensitivity (true-positives/[true-positives + false-negatives] $\times 100$ ) and specificity (true-negatives/[true-negatives + false-positives] $\times 100$ ) at  $T_5$  to  $T_{25}$  were calculated and compared with those of the  $T_{30}$  samples (the 'gold standard').

Upper gastrointestinal endoscopy was performed on 67 patients (35 female, 32 male) before the  $^{13}\text{C}$  UBT. During the examination, three biopsy specimens each from the gastric antrum and corpus were obtained for histology and bacterial culture. Silver staining (Warthin-Starry) was used to identify *H pylori* in the biopsy specimens. Culture samples were inoculated in *Brucella* blood agar, Mueller-Hinton sheep blood agar and egg yolk emulsion; all plates were incubated at 35°C for four days. *H pylori* growth was confirmed by Gram staining, a rapid urea test, an oxidase test and a wet preparation for motility. Negative cultures were reincubated and examined seven to 10 days later. Infection status was determined when both methods (histology and culture) produced concordant results. Sensitivity and specificity for all time intervals were calculated and compared with histology and culture.

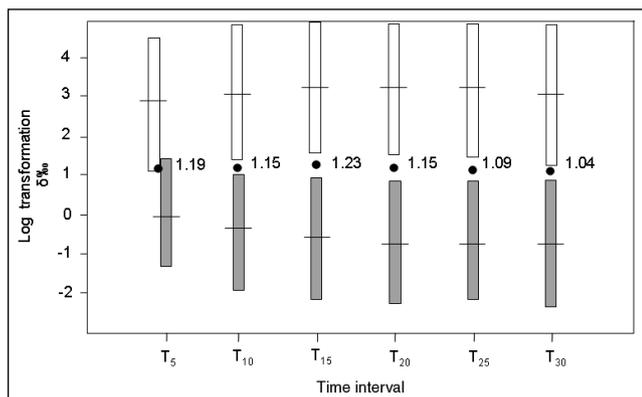
## RESULTS

Data were examined visually by plotting the logarithmic transformation of the DOB values from 297  $^{13}\text{C}$  UBT results for  $T_5$  to  $T_{30}$ . It was evident that the normal distribution of the DOB values for each time interval could describe two distinct classes: *H pylori*-negative and *H pylori*-positive populations (Figure 1). From this, the mean and SD DOB values of logn ( $T_{\text{sample interval}} - T_0$ ) for the presumed subpopulations were calculated. The point equidistant between the mean values of the subpopulations was calculated for each breath sample test interval. The optimal cut-off points determined for each time interval were 3.29  $\delta\%$  for  $T_5$ , 3.15  $\delta\%$  for  $T_{10}$ , 3.42  $\delta\%$  for  $T_{15}$ , 3.17  $\delta\%$  for  $T_{20}$ , 2.99  $\delta\%$  for  $T_{25}$  and 2.82  $\delta\%$  for  $T_{30}$  (Table 1). The difference (normal deviate) between the cut-off points and the means of normal *H pylori*-negative and *H pylori*-positive distributions were 1.90 SD for  $T_5$ , 2.21 SD for  $T_{10}$ , 2.38 SD for  $T_{15}$ , 2.41 SD for  $T_{20}$ , 2.36 SD for  $T_{25}$  and 2.17 SD for  $T_{30}$ . These normal deviates were found to be greater than 2 SD for all time intervals except for  $T_5$  (Figure 2), indicating that, by comparison of these values with the table of the proportions of the normal curve, the proportions of *H pylori*-negative and *H pylori*-positive populations producing a  $^{13}\text{C}$  UBT result greater or smaller than the cut-off point were always lower than 2.3%. Thus, except for  $T_5$ , the risks of false-positive or false-negative results from the  $^{13}\text{C}$  UBT for a diagnosis of *H pylori* infection were lower than 2.3% when using these cut-off points. When the cut-off points

**TABLE 1**  
Calculated cut-off point for each sample interval

<sup>13</sup> C UBT sample interval	Log-transformed cut-off point (‰)	Cut-off point (‰)
T <sub>5</sub>	1.19	3.29
T <sub>10</sub>	1.15	3.15
T <sub>15</sub>	1.23	3.42
T <sub>20</sub>	1.15	3.17
T <sub>25</sub>	1.09	2.99
T <sub>30</sub>	1.04	2.82

T Time past baseline (min); UBT Urea breath test



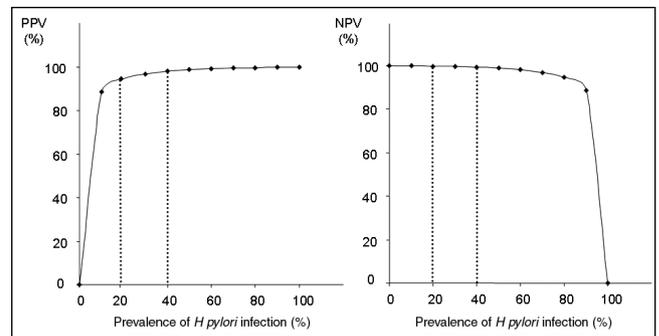
**Figure 2** The distance between the cut-off point (black circles) and the means of the *Helicobacter pylori*-positive (white bars: mean  $\pm$  2 SD) and *H pylori*-negative (grey bars: mean  $\pm$  2 SD) populations was greater than 2 SD for all sample intervals except for the time interval at 5 min past baseline (T<sub>5</sub>). Log Logarithmic

determined for T<sub>10</sub> to T<sub>30</sub> were replaced with a practical cut-off point of 3.0 ‰, the corresponding normal deviates for *H pylori*-negative and *H pylori*-positive distributions were greater than 2 SD in all cases. Thus, according to the table of the proportions of the normal curve, the risk of error was still lower than 2.3%. When a cut-off point of 3.0 ‰ was used, 25.6% of patients had positive results for *H pylori* infection.

These calculations were also performed for the two subgroups (diagnosis and confirmation of eradication). When the cut-off points obtained in the two groups were replaced with 3.0 ‰ for <sup>13</sup>C UBT T<sub>10</sub> to T<sub>30</sub>, as determined for the whole population, the normal deviates for *H pylori*-positive and *H pylori*-negative distributions in both groups were greater than 1.94 SD in all cases for all time intervals from 10 min to 30 min, showing a risk lower than 3% of false-positive or false-negative results. T<sub>10</sub> was chosen for further comparisons because it was the shortest time interval that showed a risk of error lower than 2.3%.

<sup>13</sup>C UBT results at T<sub>10</sub> were compared with those of T<sub>30</sub>, (the standard time interval). T<sub>10</sub> results showed 98.6% sensitivity and 98.6% specificity compared with T<sub>30</sub> results using a cut-off point of 3.0 ‰.

In a group of 67 patients, the T<sub>10</sub> and T<sub>30</sub> <sup>13</sup>C UBT results at a cut-off point of 3.0 ‰ were compared with histology and culture (the gold standard). The T<sub>30</sub> <sup>13</sup>C UBT showed sensitivity of 100% and specificity of 96% and the T<sub>10</sub> <sup>13</sup>C UBT



**Figure 3** Positive predictive values (PPV) and negative PV (NPV) for the <sup>13</sup>C urea breath test at 10 min past baseline. Based on a *Helicobacter pylori* prevalence of 20% to 40% in the Canadian population, the PPV at 10 min past baseline would be between 94.6% and 97.9% and the NPV would be between 99.6% and 99%

showed sensitivity of 100% and specificity of 96%. Based on an *H pylori* prevalence of 20% to 40% in the Canadian population (2,3), the positive predictive value for the T<sub>10</sub> <sup>13</sup>C UBT would be between 94.6% and 97.9% and the negative predictive value would be between 99.6% and 99% (Figure 3).

## DISCUSSION

*H pylori* has been shown to infect over 50% of the world's population, with an incidence of up to 80% in developing countries (1). Because of the pivotal role of *H pylori* in many human gastroduodenal pathologies, it has been recommended that patients with abdominal discomfort undergo a rapid, noninvasive screening for *H pylori* infection (8). The <sup>13</sup>C UBT is now widely used to document *H pylori* infection (13) and has been recommended as the preferred method for epidemiological studies and for screening patients with dyspeptic symptoms. It has also been acknowledged as the best noninvasive test to assess the efficacy of anti-*H pylori* treatments (14,15).

To render the test less expensive and more rapid, we proposed to reduce the sample interval from the standard 30 min to 10 min, with the aim of shortening sampling time to improve patient compliance and optimize personnel employment.

Using cluster analysis, we determined the cut-off points for the T<sub>10</sub> and T<sub>30</sub> samples. We found that the optimal cut-off point in our population was 3.15 ‰ for T<sub>10</sub> and 2.82 ‰ for T<sub>30</sub>. We previously validated (pages 770-774 in the current issue of the *Journal*) a cut-off point of 3.0 ‰ in a large data set data (n=2232) in a Canadian community laboratory setting. The present study indicates a lower cut-off point than that reported in previous studies (T<sub>30</sub>-T<sub>0</sub>=5.0 ‰) (16,17), but it has been confirmed by others in comparison with histology (18) and by cluster analysis (19). The risk of a false-negative or false-positive response is less than 2.3% when using a cut-off point of 3.0 ‰ for the T<sub>10</sub> and the T<sub>30</sub> samples. The risk of error was also less than 3% if the same cut-off point was used in the groups that came for diagnosis and for confirmation of cure; thus, depending on the clinical situation (before or after treatment), it appears unnecessary to use different cut-off points. Like others (19), we recommend an indeterminate zone (2.5 ‰ and 3.5 ‰) for the <sup>13</sup>C UBT, in which a second test would be recommended to assess the patient's *H pylori* status more accurately rather than using a very strict cut-off point. Only

one (of 297) result of the T<sub>10</sub> samples and two (of 297) results of the T<sub>30</sub> samples fell into this indeterminate zone.

In a group of 67 patients, the T<sub>10</sub> and T<sub>30</sub> <sup>13</sup>C UBT results at a cut-off point of 3.0 ‰ were compared with histology and culture. The T<sub>30</sub> <sup>13</sup>C UBT showed sensitivity of 100% and specificity of 96%, while the T<sub>10</sub> <sup>13</sup>C UBT showed sensitivity of 100% and specificity of 96%.

Overall, the T<sub>10</sub> <sup>13</sup>C UBT protocol in 297 individuals showed 98.6% sensitivity and 98.6% specificity compared with the 30 min <sup>13</sup>C UBT protocol. This is consistent with the results of a previous study (20) that showed absolute concordance between results obtained at 10 min in comparison with the standard results obtained at 30 min using a cut-off point of 5.0 ‰. In the present study, this diagnostic accuracy was maintained even with a lower cut-off point of 3.0 ‰. Based on an *H pylori* prevalence of 20% to 40% in the Canadian population (1,2,21), the positive predictive value for the 10 min <sup>13</sup>C UBT would be between 94.6% and 97.9% and the negative predictive value would be between 99.6% and 99% (Figure 3).

We conclude that the 10 min sample <sup>13</sup>C UBT is an accurate, noninvasive test of active *H pylori* infection. The use of a shorter test protocol has the potential to facilitate routine clinical practice and increase patient acceptance with no loss of test performance for *H pylori* management. The present study confirms the validity of the (T<sub>30</sub>-T<sub>0</sub>) and (T<sub>10</sub>-T<sub>0</sub>)=3.0 ‰ cut-off point for the diagnosis and confirmation of eradication of *H pylori* infection and underlines the necessity of an indeterminate zone between 2.5 ‰ and 3.5 ‰ in which the risk of error in this test is maximal.

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